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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Combination of Squalene Synthetase Inhibitor and Other Type of Serum Cholesterol Reducing Agent and Method for Lowering Serum Cholesterol Using Such Combination

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(57) 16 Claims

Abstract

COMBINATION OF A SQUALENE SYNTHETASE INHIBITOR AND OTHER TYPE OF SERUM CHOLESTEROL REDUCING AGENT AND METHOD FOR LOWERING SERUM CHOLESTEROL USING SUCH COMBINATION

A pharmaceutical combination is provided which includes an inhibitor of the enzyme squalene synthetase and a pharmaceutical which reduces serum cholesterol by a mechanism other than inhibiting production of the enzyme HMG CoA reductase or the enzyme squalene synthetase, namely, an antihyperlipoproteinemic agent or antihyperlipemic agent, for example, probucol or gemfibrozil. A method for reducing serum cholesterol or inhibiting formation of or treating atherosclerosis using the above combination is also provided.

COMBINATION OF SQUALENE SYNTHETASE INHIBITOR AND OTHER TYPE OF SERUM CHOLESTEROL REDUCING AGENT AND METHOD FOR LOWERING SERUM CHOLESTEROL USING SUCH COMBINATION

The present invention relates to a combination of an inhibitor of squalene synthetase and a pharmaceutical which reduces serum cholesterol other than by inhibiting squalene synthetase, and to a method for lowering serum cholesterol and/or preventing or treating atherosclerosis by administering such combination.

There are several different classes of compounds which have serum cholesterol lowering properties. Some of these compounds are inhibitors of the enzyme HMG CoA reductase which is essential in the production of cholesterol, such as mevastatin (disclosed in U. S. Patent No. 3,983,140), lovastatin also referred to as mevinolin (disclosed in U. S. Patent No. 4,231,938), pravastatin (disclosed in U. S. Patent No. 4,346,227) and velostatin also referred to as synvinolin (disclosed in U. S. Patents Nos. 4,448,784 and 4,450,171).

Other compounds which lower serum cholesterol may do so by an entirely different mechanism than the HMG CoA reductase inhibitors. For example, serum cholesterol may be lowered through the use of bile acid sequestrants such as cholestyramine, colestipol, DEAE-Sephadex and poly(diallylmethylamine) derivatives (such as disclosed in U. S. Patents Nos. 4,759,923 and 4,027,009) or through the use of antihyperlipoproteinemics such as probucol and gemfibrozil which apparently lower serum "low density lipoproteins" (LDL) and/or convert LDL into high density lipoproteins (HDL).

U. S. Patent No. 4,759,923 mentioned above discloses that poly(diallylmethylamine) derivatives which are bile salt sequestrants may be used in conjunction with drugs which reduce serum cholesterol by mechanisms other than sequestration, such as clofibrate, nicotinic acid, probucol, neomycin, p-aminosalicylic acid or mevinolin (also referred to as lovastatin).

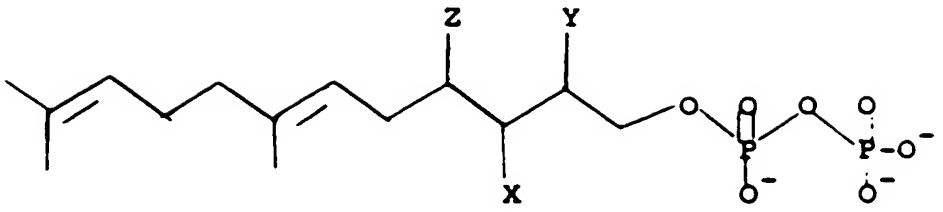
Squalene synthetase is a microsomal enzyme which catalyzes the reductive dimerization of two molecules of farnesyl pyrophosphate (FPP) in the presence of nicotinamide adenine dinucleotide phosphate (reduced form) (NADPH) to form squalene (Poulter, C. D.; Rilling, H. C., in "Biosynthesis of Isoprenoid Compounds", Vol. I, Chapter 8, pp. 413-441, J. Wiley and Sons, 1981 and references therein). This enzyme is the first committed step of the de novo cholesterol biosynthetic pathway. The selective inhibition of this step should allow the essential pathways to isopentenyl tRNA,

ubiquinone, and dolichol to proceed unimpeded. Squalene synthetase, along with HMG-CoA reductase has been shown to be down-regulated by receptor mediated LDL uptake (Faust, J. R.; Goldstein, J. L.; Brown, M. S. Proc. Nat. Acad. Sci. USA, 1979, 76, 5018-5022), lending credence to the proposal that inhibiting squalene synthetase will lead to an up-regulation of LDL receptor levels, as has been demonstrated for HMG-CoA reductase, and thus ultimately should be useful for the treatment and prevention of hypercholesterolemia and atherosclerosis.

One approach to inhibitors of squalene synthetase is to design analogs of the substrate FPP. It is clear from the literature that the pyrophosphate moiety is essential for binding to the enzyme. However, such pyrophosphates are unsuitable as components of pharmacological agents due to their chemical and enzymatic lability towards allylic C-O cleavage, as well as their susceptibility to metabolism by phosphatases.

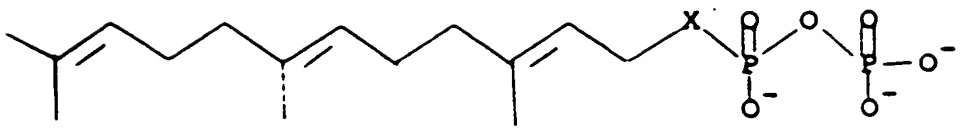
P. Ortiz de Montellano et al. in J. Med. Chem., 1977, 20, 243-249 describe the preparation of a series of substituted terpenoid pyrophosphates (Table A), and have shown these to be competitive inhibitors of the squalene synthetase enzyme. These substances retain the unstable allylic pyrophosphate moiety of FPP.

Table A

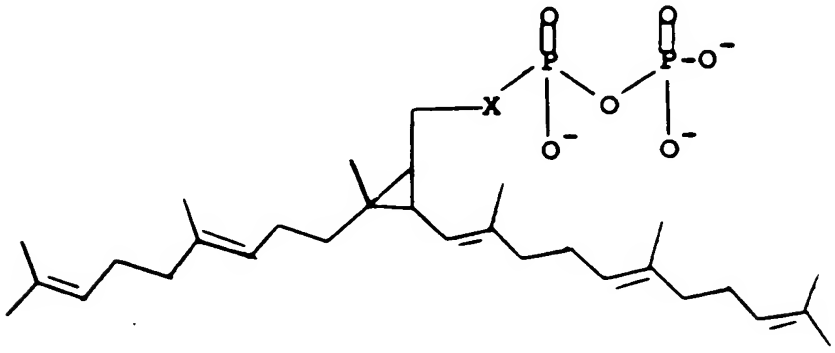


No.	X	Y	Z
1	CH_3	CH_3	H
2	H	H	H
3	C_2H_5	H	H
4	I	H	H
5	H	I	H
6	CH_3	H	SCH_3

Corey and Volante, J. Am. Chem. Soc. 1976, 98, 1291-3, have prepared FPP analog A and presqualene pyrophosphate (PSQ-PP) analog B as inhibitors of squalene biosynthesis. (Presqualene pyrophosphate is an intermediate in the conversion of FPP to squalene). These inhibitors possess methylene groups in place of the allylic oxygen moiety of FPP and PSQ-PP, but still retain the chemically and enzymatically unstable pyrophosphate linkage.

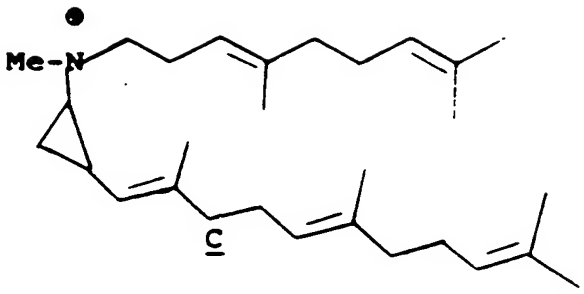


A X = CH_2
FPP X = O



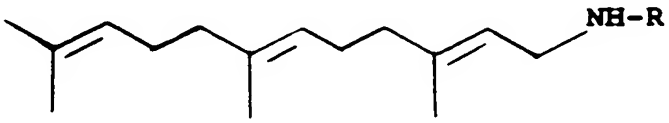
B X = CH_2
PSQ-PP X = O

Poulter and co-workers have prepared cyclopropane C (Sandifer, R. M., et al., J. Am. Chem. Soc. 1982, 104, 7376-8) which in the presence of inorganic pyrophosphate is an intermediate analog inhibitor of the enzyme squalene synthetase.



C

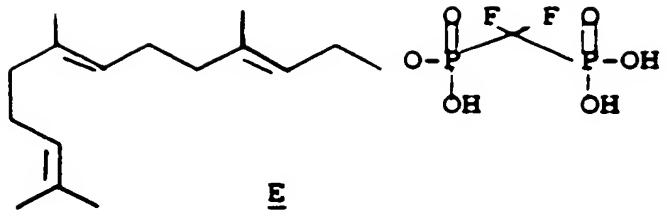
Altman and co-workers, Bertolino, A., et al., Biochim. Biophys. Acta. 1978, 530, 17-23, reported that farnesyl amine and related derivatives D inhibit squalene synthetase, but provide evidence that this inhibition is non-specific and probably related to membrane disruption.



R = H, CH_2CH_2OH, $CH_2CH_2OCH_3$

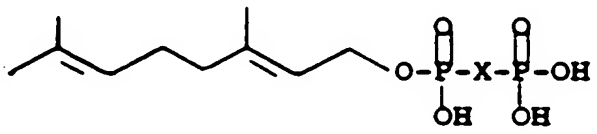
D

Poulter, C.D., et al, J. Org. Chem., 1986, 51, 4768, prepared compound E in a demonstration of a synthetic method, but did not report any biological data.



E

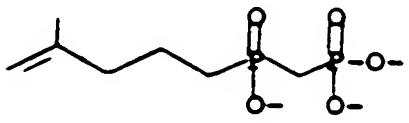
Poulter, C.D., Stremler, K.E., J.A.C.S., 1987, 109, 5542 describes the synthesis and biological evaluation of compounds having structure F. These compounds were evaluated as alternative substrates for avian liver farnesyl diphosphate and lemon peel cyclase.



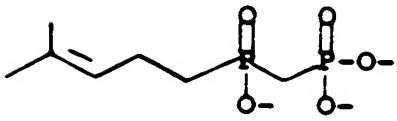
F X=CH_2, CF_2

McClard, R. W. and Poulter, C. D., et al., J.A.C.S. 1987, 109, 5544, reported that phosphinylphosphonates G and H were competitive inhibitors of the 1'-4-condensation between isopentenyl diphosphate and geranyl diphosphate catalyzed by avian liver farnesyl diphosphate synthetase. Phosphinylphosphonates G and H had Ki's of 19μM and 71μM, respectively. They also reported the speculative isolation of the farnesyl phosphinylphosphonate I, and the geranyl phosphinylphosphonate J from the enzymatic reaction of G with g ranyl pyrophosphate or dimethylallyl

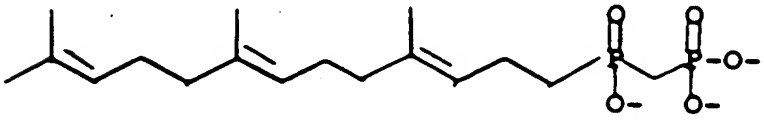
pyrophosphate, respectively. The structures of I and J were tentatively assigned based on relative TLC mobilities. They hypothesized that I could be a potential inhibitor of squalene synthetase.



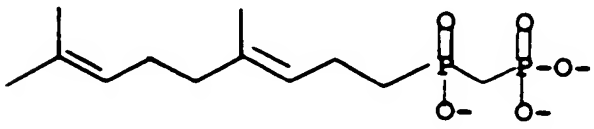
G



H

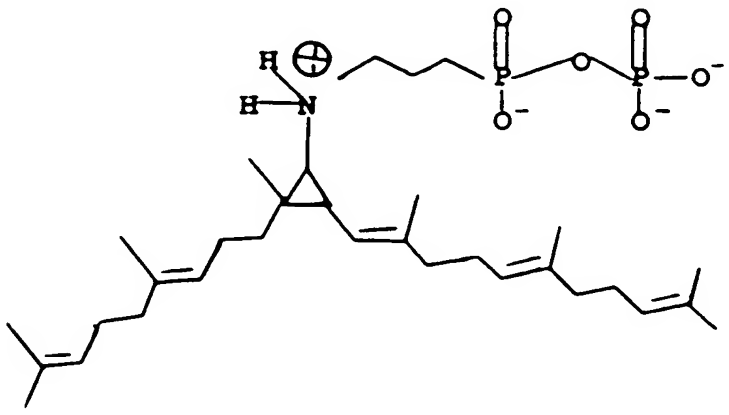


I



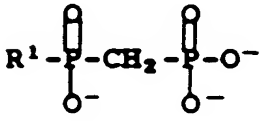
J

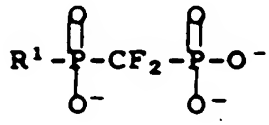
Capson, T.L., PhD dissertation, June 1987, Dept. of Medicinal Chemistry, the University of Utah, Abstract, Table of Contents, pp. 16, 17, 40-43, 48-51, Summary, discloses cyclopropanes of the structure



as intermediate analog inhibitors of squalene synthetase.

S. A. Biller et al., Journal of Medicinal Chemistry, 1988, Vol. 31, No. 10, pp 1869 to 1871 disclose that isoprenoid (phosphinylmethyl) phosphonates (PMPs) inhibit squalene synthetase. These phosphonates have the structures

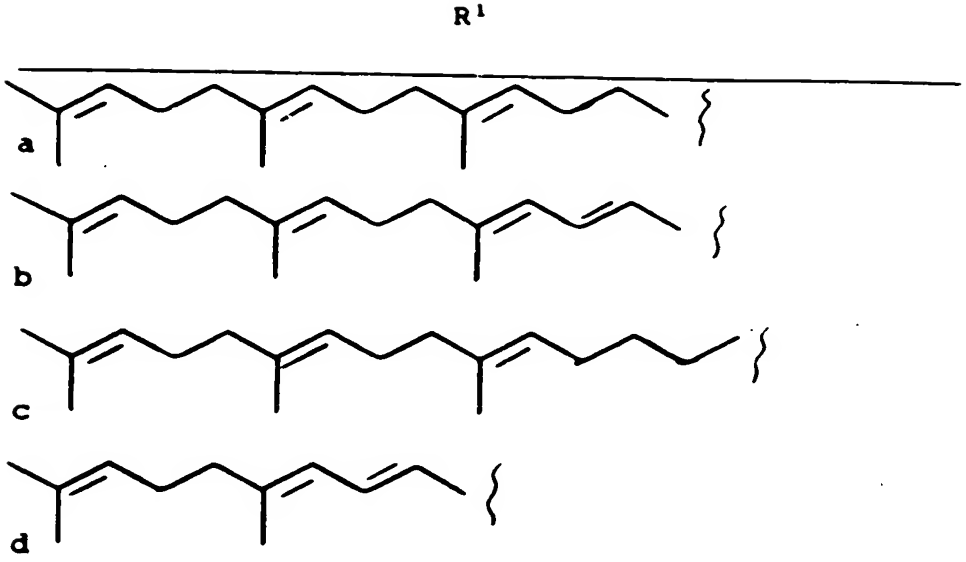




2a-d

3a,b

R^1



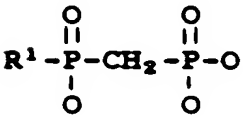
In accordance with the present invention, a pharmaceutical combination is provided for use in reducing serum cholesterol and in inhibiting formation of, or treating atherosclerosis, which combination is formed of an inhibitor of the enzyme squalene synthetase and a pharmaceutical (also referred to as other serum cholesterol lowering agent) which reduces serum cholesterol and/or inhibits cholesterol biosynthesis by a mechanism other than by inhibiting production of the enzyme squalene synthetase or 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG CoA) reductase, such as a bile salt sequestrant or antihyperlipoproteinemic agent which inhibits formation of LDL or converts LDL to HDL. The squalene synthetase inhibitor will be employed in a weight ratio to the "pharmaceutical" of within the range of from about 0.001:1 to about 1000:1 and preferably from about 0.05:1 to about 100:1.

In addition, in accordance with the present invention, a method is provided for low ring serum cholesterol or inhibiting formation of or treating

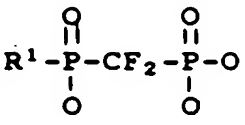
atherosclerosis wherein a therapeutically effective amount of the above combination is systemically, such as orally or parenterally, administered over a prolonged period.

The combination of the squalene synthetase inhibitor and other serum cholesterol lowering agent, as described above, is a surprising and unique concept in inhibiting or treating elevated cholesterol and/or atherosclerosis in that it may provide additional anticholesterolemic effects over that which may be obtained using each of the components of the combination alone. In addition, the combination of the invention which includes compounds with different mechanisms of action, may be used to effectively treat cholesterol-related diseases of multiple etiology.

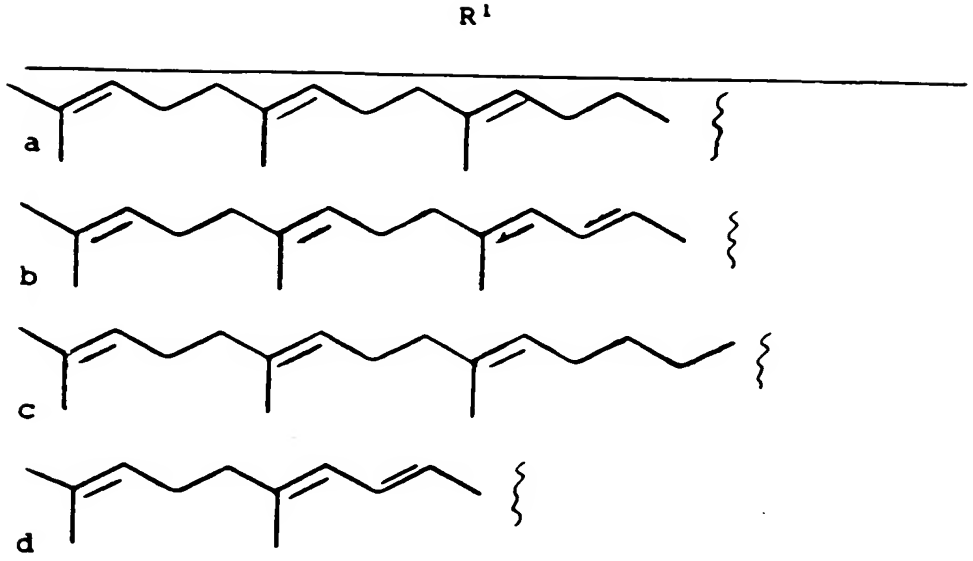
The squalene synthetase inhibitors suitable for use herein include, but are not limited to, those disclosed by Biller et al., supra, including isoprenoid (phosphinylmethyl)phosphonates such as those of the formula



I



II



including the triacids thereof, triesters thereof and tripotassium and trisodium salts thereof as well as other squalene synthetase inhibitors disclosed in pending U.S. patent application Serial No. 141,744, filed January 11, 1988.

In addition, other squalene synthetase inhibitors suitable for use herein include the terpenoid pyrophosphates disclosed by P. Ortiz de Montellano et al., J. Med. Chem.; 1977, 20, 243-249, the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and Volante, J. Am. Chem. Soc. 1976, 98, 1291-1293, phosphinylphosphonates reported by McClard, R. W. et al., J.A.C.S., 1987, 109, 5544 and cyclopropanes reported by Capson, T.L., PhD dissertation, June, 1987, Dept. Med. Chem. U. of Utah, abstract, Table of Contents, pp. 16, 17, 40-43, 48-51, Summary, as well as other known squalene synthetase inhibitors.

The "pharmaceutical" or other serum cholesterol lowering agents which function other

than by inhibiting the enzyme HMG CoA reductase or squalene synthetase suitable for use herein include, but are not limited to, antihyperlipoproteinemic agents such as probucol, and gemfibrozil and related compounds as disclosed in U. S. Patent No. 3,674,836, probucol and gemfibrozil being preferred, bile acid sequestrants such as cholestyramine, colestipol and DEAE-Sephadex (Secholex®, Polidexide®), as well as clofibrate, lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402) tetrahydrolipstatin (THL), istigmastanyl-phosphorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (di-substituted urea derivatives), nicotinic acid, neomycin, p-aminosalicylic acid, aspirin, poly(diallylmethylamine) derivatives such as disclosed in U. S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes such as disclosed in U. S. Patent No. 4,027,009, and other known serum cholesterol lowering agents which lower cholesterol through a mechanism other than by the inhibition of the enzyme HMG CoA reductase or squalene synthetase.

Preferred are combinations of any of the isoprenoid (phosphinylmethyl) phosphonates disclosed by Biller et al., supra with probucol or gemfibrozil.

The disclosure of the above-mentioned patents and patent applications are incorporated herein by reference.

In carrying out the method of the present invention, the combination of the invention may be administered to mammalian species, such as monkeys, dogs, cats, rats, humans, etc. and as such may be incorporated in a conventional systemic dosage form, such as a tablet, capsule, elixir or injectable. The above dosage forms will also include the necessary carrier material, excipient, lubricant, buffer, antibacterial, bulking agent (such as mannitol), anti-oxidants (ascorbic acid or sodium bisulfite) or the like. Oral dosage forms are preferred, although parenteral forms are quite satisfactory as well.

The dose administered must be carefully adjusted according to age, weight and condition of the patient, as well as the route of administration, dosage form and regimen and the desired result.

Thus, for oral administration, a satisfactory result may be obtained employing the squalene synthetase inhibitor in dosages in an amount within the range of from about 10 to about 2000 mg and preferably from about 25 to about 200 mg in combination with the other serum cholesterol lowering agent in dosages normally employed as indicated in the Physician's Desk Reference, for each of such agents such as in an amount within the range of from about 2 mg to about 7500 mg and preferably from about 2 mg to about 4000 mg with the squalene synthetase inhibitor and other serum cholesterol lowering agent being employed together in the same oral dosage form or in separate oral dosage forms taken at the same time.

A preferred oral dosage form, such as tablets or capsules, will contain the squalene synthetase inhibitor in an amount of from about 10 to about 500 mg, preferably from about 25 to about 200 mg, and the other serum cholesterol lowering agent in an amount of from about 2 to about 3000 mg, preferably from about 2 to about 2000 mg.

The composition described above may be administered in the dosage forms as described above in single or divided doses of one to four times daily. It may be advisable to start a patient on a low dose combination and work up gradually to a high dose combination.

Tablets of various sizes can be prepared, e.g., of about 2 to 2000 mg in total weight, containing one or both of the active substances in the ranges described above, with the remainder being a physiologically acceptable carrier of other materials according to accepted pharmaceutical practice. These tablets can, of course, be scored to provide for fractional doses. Gelatin capsules can be similarly formulated.

Liquid formulations can also be prepared by dissolving or suspending one or the combination of active substances in a conventional liquid vehicle acceptable for pharmaceutical administration so as to provide the desired dosage in one to four teaspoonsful.

Such dosage forms can be administered to the patient on a regimen of one to four doses per day.

According to another modification, in order to more finely regulate the dosage schedule, the active substances may b administered separately in

individual dosage units at the same time or carefully coordinated times. Since blood levels are built up and maintained by a regulated schedule of administration, the same result is achieved by the simultaneous presence of the two substances. The respective substances can be individually formulated in separate unit dosage forms in a manner similar to that described above.

Fixed combinations of squalene synthetase inhibitor and other serum cholesterol lowering agent are more convenient and are preferred, especially in tablet or capsule form for oral administration.

In formulating the compositions, the active substances, in the amounts described above, are compounded according to accepted pharmaceutical practice with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in the particular type of unit dosage form.

Illustrative of the adjuvants which may be incorporated in tablets are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as dicalcium phosphate or cellulose; a disintegrating agent such as corn starch, potato starch, alginic acid or the like; a lubricant such as stearic acid or magnesium stearate; a sweetening agent such as sucrose, aspartame, lactose or saccharin; a flavoring agent such as orange, peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contain in addition to materials of the above type a liquid carrier such as a fatty oil. Various

other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets or capsules may be coated with shellac, sugar or both. A syrup of elixir may contain the active compound, water, alcohol or the like as the carrier, glycerol as solubilizer, sucrose as sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange.

Some of the active substances described: above form commonly known, pharmaceutically acceptable salts such as alkali metal and other common basic salts or acid addition salts, etc. References to the base substances are therefore intended to include those common salts known to be substantially equivalent to the parent compound.

The formulations as described above will be administered for a prolonged period, that is, for as long as the potential for elevated serum cholesterol and atherosclerosis remains or the symptoms continue. Sustained release forms of such formulations which may provide such amounts biweekly, weekly, monthly and the like may also be employed. A dosing period of at least one to two weeks are required to achieve minimal benefit.

The following Examples represent preferred embodiments of the present invention. All temperatures are expressed in degrees Centigrade unless otherwise indicated and all mesh sizes are U.S. Standard ASTME.

Example 1

A squalene synthetase inhibitor formulation in the form of tablets having the following composition was prepared as described below.

Ingredient	Weight (mg)
(E,E)-[[hydroxy(4,8,12-trimethyl-3,7,11-tridecatrienyl)phosphinyl]-methyl]phosphonic acid tripotassium salt (squalene synthetase inhibitor prepared as described by Biller et al. supra)	100 mg
Cornstarch	50 mg
Gelatin	7.5 mg
Avicel (microcrystalline cellulose)	25 mg
Magnesium stearate	2.5 mg
	185 mg

The tablets are prepared from sufficient bulk quantities by mixing the tripotassium salt and cornstarch with an aqueous solution of the gelatin. The mixture is dried and ground to a fine powder. The Avicel and then the magnesium stearate are admixed with granulation. The mixture is compressed in a tablet press to form tablets each containing 100 mg of active ingredient.

Probucol tablets containing 250 mg probucol are prepared employing conventional procedures containing the following additional ingredients as set out in the 1988 PDR: corn starch, ethyl cellulose, glycerin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose 2910, iron oxide, lactose, magnesium stearate, microcrystalline cellulose, polysorbate 80, talc and titanium dioxide.

The squalene synthetase inhibitor and probucol tablets may be administered as a combination in accordance with the teachings of the present invention to lower serum cholesterol and/or treat atherosclerosis. In addition, the squalene synthetase inhibitor and probucol tablets may be ground up into powders and used together in a single capsule.

Example 2

Tablets each containing the following ingredients:

Ingredient	Weight (mg)
(E,E)-[difluoro[hydroxy(4,8,12-trimethyl-3,7,11-tridecatrienyl)-phosphinyl]methyl]phosphonic acid tripotassium salt (squalene synthetase inhibitor prepared as described by Biller et al. supra)	100 mg
Avicel	112.5 mg
Lactose	113 mg
Cornstarch	17.5 mg
Stearic Acid	7 mg
	350 mg

are prepared from sufficient bulk quantities by slugging the squalene synthetase inhibitor, Avicel, and a portion of the stearic acid. The slugs are ground and passed through a #2 screen and then mixed with the lactose, cornstarch, and the remainder of stearic acid. The mixture is compressed into 350 mg capsule shaped tablets in a tablet press. The tablets are scored for dividing in half.

Capsules containing 300 mg gemfibrozil are prepared employing conventional pharmaceutical techniques containing the following additional ingredients as described in the 1988 PDR: polysorbate 80 NF, starch NF and silica gel.

The squalene synthetase inhibitor tablet and gemfibrozil capsule may be administered as a combination or the squalene synthetase inhibitor tablet may be ground into a powder and used in a single capsule containing gemfibrozil to lower

s rum cholesterol and/or treat atherosclerosis in accordance with the teachings of the present invention.

Examples 3

A formulation in the form of tablets having the following composition was prepared as described in Example 1.

Ingredient	Weight (mg)
(E,E,E)-[difluoro[hydroxy(4,8,12-trimethyl-1,3,7,11-tridecatetraenyl)phosphinyl]methyl]-phosphonic acid tripotassium salt (squalene synthetase inhibitor prepared as described by Biller et al. supra)	100 mg
Cornstarch	50 mg
Gelatin	7.5 mg
Avicel (microcrystalline cellulose)	25 mg
Magnesium stearate	2.5 mg
	185 mg

The above squalene synthetase inhibitor tablets may be employed in combination with clofibrate capsules containing 500 mg clofibrate and inactive ingredients including color, and gelatin as described in the 1988 PDR. The squalene synthetase inhibitor and clofibrate may be employed in separate dosage forms or combined in a single capsule form to lower elevated serum cholesterol or treat atherosclerosis in accordance with the present invention.

Exampl s 4 to 6

Squalene synthetase inhibitor tablets described in Examples 1, 2 and 3, respectively, may be employed in combination with cholestyramine resin containing 4 g cholestyramine, acacia, citric acid, color, flavor, polysorbate 80, propylene glycol alginate and sucrose as described in the 1988 PDR. The squalene synthetase inhibitor and cholestyramine may be employed in separate dosage forms or combined in a single capsule form to lower serum cholesterol or treat atherosclerosis in accordance with the present invention.

Examples 7 to 10

Squalene synthetase inhibitor tablets, prepared as described in Examples 1, 2 and 3, respectively, may be employed in combination with nicotinic acid, colestipol, dextrothyroxine or other serum cholesterol lowering agent in accordance with the teaching of the present invention to lower cholesterol or treat atherosclerosis.

It will also be appreciated that any of the squalene synthetase inhibitors disclosed in the Biller et al. paper and in pending U.S. patent application Serial No. 141,744 may be employed in combination with any of the serum cholesterol lowering agents disclosed herein in accordance with the present invention.

What we claim is:

1. A pharmaceutical combination comprising an inhibitor of the enzyme squalene synthetase and a pharmaceutical which reduces serum cholesterol and/or inhibits cholesterol biosynthesis by a mechanism other than inhibiting production of the enzyme HMG CoA reductase or squalene synthetase.

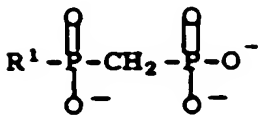
2. The combination as defined in Claim 1 wherein said pharmaceutical is an antihyperlipoproteinemic agent or antihyperlipemic agent.

3. The combination as defined in Claim 2 wherein said antihyperlipoproteinemic agent or antihyperlipemic agent is probucol, gemfibrozil, clofibrate, dextrothyroxine or its sodium salt, colestipol or its hydrochloride, cholestyramine, nicotinic acid, neomycin, p-aminosalicylic acid or aspirin.

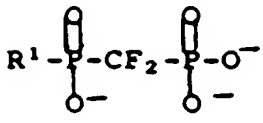
4. The combination as defined in Claim 1 wherein said pharmaceutical is a bile acid sequestrant.

5. The combination as defined in Claim 4 wherein said bile acid sequestrant is cholestyramine, colestipol, DEAE-Sephadex, a poly(diallylmethylamine) derivative, an ionene or the quaternary amine poly(diallyldimethylammonium) chloride.

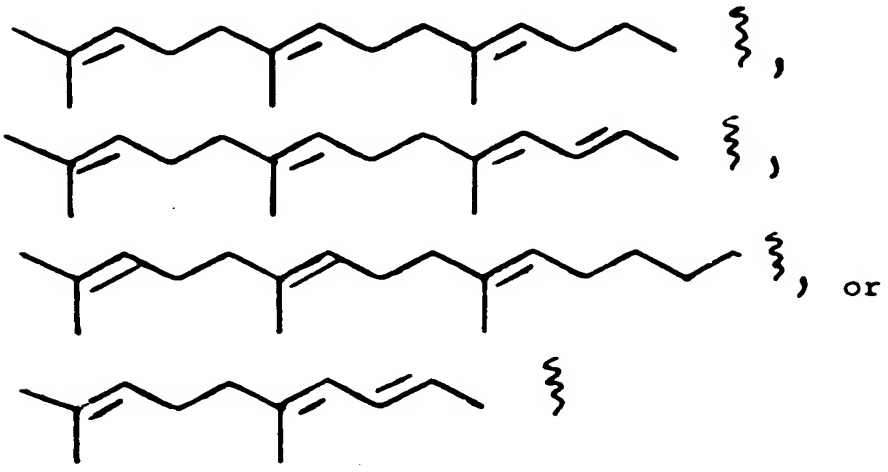
6. The combination as defined in Claim 1 wherein said inhibitor of the enzyme squalene synthetase has the formula



or



wherein R^1 is



7. The combination as defined in CLaim 1 wherein the inhibitor of the enzyme squalene synthetase is present in a weight ratio to said pharmaceutical of within the range of from about 0.001:1 to about 1000:1.

8. The combination as defined in Claim 6 wherein said pharmaceutical is probucol, gemfibrozil, nicotinic acid, cholestyramine, clofibrate, colestipol or p-aminosalicyclic acid.

9. The combination as defined in Claim 6 wherein said pharmaceutical is probucol or gemfibrozil.

10. A method for lowering serum cholesterol or inhibiting formation of or treating atherosclerosis, which comprises administering to a patient in need of such treatment a therapeutically effective amount of a pharmaceutical combination comprising an inhibitor of the enzyme squalene synthetase and a pharmaceutical which reduces serum cholesterol by a mechanism other than inhibiting production of the enzymes squalene synthetase and HMG CoA reductase.

11. The method as defined in Claim 10 wherein said pharmaceutical is an antihyperlipoproteinemic agent or antihyperlipemic agent.

12. The method as defined in Claim 11 wherein said antihyperlipoproteinemic agent or antihyperlipemic agent is probucol, gemfibrozil, clofibrate, dextrothyroxine or its sodium salt, colestipol or its hydrochloride, cholestyramine, nicotinic acid, neomycin, p-aminosalicylic acid or aspirin.

13. The method as defined in Claim 10 wherein said pharmaceutical is a bile acid sequestrant.

14. The method as defined in Claim 13 wherein said bile acid sequestrant is cholestyramine, colestipol, DEAE-Sephadex, a poly(diallylmethylamine) derivative, an ionene or the quaternary amine poly(diallyldimethylammonium) chloride.

15. The method as defined in Claim 10 wherein said pharmaceutical is probucol, gemfibrozil, nicotinic acid, cholestyramine, clofibrate, colestipol or p-aminosalicyclic acid.

16. A hypocholesterolemic or hypolipemic composition comprising a combination as defined in Claim 1 and a pharmaceutically acceptable carrier therefor.